UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/291,925	04/14/99	ASHKENAZI	A	P1055R1

HM22/0523

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EXAMINER	
ZEMAN, R	
ART UNIT	**PAPER NUMBER**
1645	18

DATE MAILED: 05/23/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/291,925	Ashkenazi et al.
Examiner	**Art Unit**
Robert A. Zeman	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 2, 2001* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *2-5 and 7-46* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *2-5 and 7-46* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *12*

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

The amendment filed on 3-2-01 is acknowledged. Claims 2, 5, 7, 9, 14 and 30 have been amended. Claims 1 and 6 have been canceled. Claims 34-46 have been added. Consequently, claims 2-5 and 7-46 are pending and currently under examination.

Objections Withdrawn

Specification

The objection to the specification is withdrawn. The substitute specification including claims as required has been entered.

Claim Objections

The objection to claim 9 because of an obvious grammatical error is withdrawn in light of the amendment thereto.

Claim Rejections Withdrawn

The rejection of claim 15 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for DNA constructs comprising a first DNA sequence encoding a precursor peptide and a second DNA sequence (encoding a heterologous glycoprotein) operably linked to the first DNA sequence, does not reasonably provide enablement for DNA constructs with

additional DNA segments operably linked to the first and second DNA segments is withdrawn. Applicant's arguments have been fully considered and found to be persuasive.

The rejection of claims 1-32 under 35 U.S.C. 112, second paragraph, as being indefinite by the inconsistent use of the terms "segment" and "sequence" is withdrawn in light of the cancellation of claim 1 and the amendments to claims 14 and 30.

35 USC § 102

The rejection of claim 1 is under 35 U.S.C. 102(b) as being anticipated by Foster et al. (U.S. Patent 5,641,655 IDS-5) is withdrawn. Cancellation of said claim has rendered the rejection moot.

Claim Rejections Maintained

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23 and 38 are rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth in the previous Office action in rejecting claim 23. In short, the specification, while being enabling for DNA constructs comprising a first DNA sequence encoding a precursor peptide and a second DNA sequence operably linked to the first DNA segment, wherein the second DNA

sequence encodes a heterologous glycosylation site **deletion** variant, does not reasonably provide enablement for DNA constructs comprising a first DNA sequence encoding a precursor peptide and a second DNA sequence operably linked to the first DNA sequence, wherein the second DNA segment encodes a heterologous glycosylation site **addition** or any other type of glycosylation site variant. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant argues:

1. The specification provides both general and detailed support for adding a glycosylation site to a protein (page 2, lines 16-18, page 3 lines 1-10, page 7 lines 3-10 and 14-19, and at page 13 lines 1-16).

Applicant's arguments have been fully considered and are deemed to be non-persuasive.

As outlined in the previous Office action, the specification provides great detail on the construction and use of DNA comprising a first DNA sequence comprising a precursor peptide (the pro sequence of t-PA) which is operably linked to a second DNA sequence encoding a heterologous glycoprotein (TNFR1-IgG1). The specification further discloses the use of sequences for glycosylation site variants as the second DNA sequence and methods for the recombinant expression of said DNA constructs *in vitro*. The specification provides great detail in the methods required for the manufacture and use of DNA sequences encoding a heterologous

glycosylation site **deletion** variant. The specification discloses that the chimeric proteins generated by the DNA constructs of the instant application contain 4 N-linked glycosylation sites (at amino acid positions 14, 105, 111 and 248) and that said glycosylation sites were "**deleted**" by replacing the codon specifying asparagine in the N-linked carbohydrate attachment sequence with codons specifying glutamine, aspartic acid, asparagine, lysine, serine or threonine thus inactivating the site (see pages 17 and 19). The specification discloses a myriad of different glycosylation site mutants and their secretion efficiencies. However, all the disclosed variants are glycosylation site **deletion** variants. None of the disclosed variants contain more than the 4 N-linked glycosylation sites at amino acid positions 14, 105, 111 and 248. The specification is silent not only on where the additional sites would be located but also on the methods that would be used to achieve such a site addition. Consequently, it would require **undue** experimentation by one of skill in the art to make and use the claimed invention due to the total lack of guidance within the specification. The portions of the specification cited by Applicant merely prophetically describe glycosylation site addition variants but fails to provide guidance on how to make said variants.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims 29 and 33 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained for reasons of record.

Claim 33 is still rendered vague and indefinite by the inconsistent use of the terms "segment" and "sequence". Applicant has indicated that said claim was to amended but no amendment to this claim has been received to date.

Claim 29 is rendered vague and indefinite by the use of the phrase "N-linked site at 14 deleted." It is unclear what is meant by "14". Applicant argues that since the phrase amino acid position 14 is recited in claim 28 (on which claim 29 is dependent) the meaning of the term "14" is clear. Applicant's argument has been fully considered and is deemed to be non-persuasive. It is still unclear whether applicant is referring to an amino acid position, some other type of chemical nomenclature or claim 14 (on which claim 29 is also dependent).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was

commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of claims 2-4 and 10-13 under 35 U.S.C. 103(a) as being unpatentable over Foster et al (U.S. Patent 5,641,655 IDS-5) in view of Ashkenazi et al. (PNAS Vol. 88 pages 10535-10539, 1991, IDS-5) is maintained for reasons of record.

Applicant argues:

1. The cited references do not teach all the limitations of the claimed invention.

2. There is no motivation to combine the cited references.

3. Foster et al. do not discuss the secretion of immunoadhesins or that a sequence including a pro-sequence of a mammalian t-PA could provide for secretion of an immunoadhesin.

4. Foster et al. do not discuss operably linking a mammalian t-PA pro-sequence with a non-mammalian pre-sequence.

5. Ashkenazi et al. do not discuss or suggest that TNFR-IgG is problematic or needs to be increased or that such an increase can be accomplished by including a t-PA pro-sequence.

6. Ashkenazi et al. do not discuss operably linking a mammalian t-PA pro-sequence with a non-mammalian t-PA pre-sequence.

Applicant's arguments have been fully considered and are deemed to be non-persuasive.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., a non-mammalian t-PA pre-sequence operably linked to a mammalian t-PA pro-sequence) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). As outlined in the previous Office Action, the instant claims are drawn to DNA constructs comprising a first DNA segment encoding a pro-sequence of mammalian t-PA and a second DNA segment operably linked to the first DNA segment encoding a heterologous glycoprotein (TNFR-IgG1). Foster et al. disclose DNA constructs comprising a first DNA segment encoding a secretory peptide (mammalian t-PA) joined to a second DNA segment encoding a heterologous protein (thrombopoietin). The disclosure by Foster et al. differs from the aforementioned claims in that the heterologous protein encoded by the second DNA segment is thrombopoietin, not TNFR-IgG1. Ashkenazi et al., disclose the sequence for the TNFR-IgG1.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5

USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, it would have been obvious for one of skill in the art to use the sequence for TNFR-IgG1 as the second DNA segment in the constructs disclosed by Foster et al. to take advantage of the increased secretion rates associated with the t-PA chimeras disclosed by Foster et al. It is standard practice to maximize yields.

Claims 2-5, 7-13, 34-37 and 39-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Foster et al (U.S. Patent 5,641,655 IDS-5) in view of Ashkenazi et al. (PNAS Vol. 88 pages 10535-10539, 1991, IDS-5) and Rickles et al. (Journal of Biological Chemistry Vol 263, No. 3 pages 1563-1569, 1988, IDS-5) for the reasons stated in the previous Office Action in rejecting claims 1-13.

Applicant argues:

1. The deficiencies of Foster et al. and Ashkenazi et al. are not remedied by Rickles et al.

2. Rickles et al. is directed to the isolation and purification of a cDNA encoding a murine tissue plasminogen activator. Said reference does not discuss or suggest that a sequence including a pro-sequence of a mammalian t-PA can or should be used to provide for secretion of any protein.

3. There is no discussion or suggestion that the pro-sequence of a mammalian t-PA sequence be operably linked to a non-mammalian t-PA pre-sequence.

Applicants arguments have been fully considered and are deemed to be non-persuasive.

Applicant is reminded that the aforementioned rejection is based on the **combination** of the cited references.

As outlined in the previous Office Action, the instant claims are drawn to DNA constructs comprising a first DNA segment encoding a pro-sequence of mammalian t-PA and a second DNA segment operably linked to the first DNA segment encoding a heterologous glycoprotein (TNFR-IgG1). Foster et al. disclose DNA constructs comprising a first DNA segment encoding a secretory peptide (mammalian t-PA) joined to a second DNA segment encoding a heterologous protein (thrombopoietin). Foster et al. differs from the aforementioned claims in that the heterologous protein encoded by the second DNA segment is thrombopoietin, not TNFR-IgG1. Additionally, Foster et al. does not disclose the use of non-mammalian t-PA. Ashkenazi et al. disclose the sequence for the TNFR-IgG1. Rickles et al. disclose the sequences for and the uses of murine t-PA in the molecular cloning of complementary DNA. Since Foster et al. disclose that **t-PAs from non-human sources** can be used in their method, and even listed an example (see column 9 lines 5-9) , it would have been obvious for one of skill in the art to use the sequence for TNFR-IgG1 as the second DNA segment and the non-mammalian t-PA prosequence disclosed by Rickles et al in the constructs disclosed by Foster et al. to take advantage of the increased secretion rates associated with the t-PA pro chimeras disclosed by Foster et al.

Claims 2-4, 10-14 and 16-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Foster et al (U.S. Patent 5,641,655 IDS-5) in view of Ashkenazi et al. (PNAS Vol. 88 pages

10535-10539, 1991, IDS-5) and Berman and Lasky et al. (Trends in Biotechnology, Vol. 3, No. 2, pages 51-53, 1985, IDS-5) for the reasons stated in the previous Office Action in rejecting claims 1-4, 10-14, 16-22, and 23-33.

Applicant argues:

1. Berman and Lasky do not discuss the problems of secretion of glycoproteins or that a prosequence of a mammalian t-PA be operably linked to a DNA segment encoding an immunoadhesin or operably linked to a pre-sequence other than a mammalian t-PA pre-sequence.

2. Berman and Lasky do not teach or suggest the formation of glycosylation site variants.

3. One of skill in the art would not combine the teachings of the cited references.

Applicant's arguments have been fully considered and deemed to be non-persuasive.

Applicant is reminded that the aforementioned rejection is based on the **combination** of the cited references. As outlined in the previous Office Action, Foster et al. disclose DNA constructs comprising a first DNA segment encoding a secretory peptide (mammalian t-PA) joined to a second DNA segment encoding a heterologous protein (thrombopoietin). The disclosure by Foster et al. differs from the aforementioned claims in that the heterologous protein encoded by the second DNA segment is thrombopoietin, not TNFR-IgG1. Additionally, Foster et al. does not disclose the use of glycosylation site variants as the products of the second DNA fragments. Ashkenazi et al. not only discloses the sequence for the TNFR-IgG1, but also potential asparagine-linked (N-linked) glycosylation sites (see Figure 1 on page 10536). Since, as disclosed by Berman and Lasky, N-linked glycosylation plays a role in the solubility half-life and antigenicity

of the glycoprotein, it would have been obvious for one of skill in the art to alter the codons for the potential N-linked glycosylation sites in the sequence for TNFR-IgG1 (disclosed by Ashkenazi et al.) and use the resulting sequences as the second DNA segment in the constructs disclosed by Foster et al. The use of the aforementioned "TNFR-IgG1 glycosylation variants" would not only take advantage of the increased secretion rates associated with the t-PA pro chimeras disclosed by Foster et al. but would allow for the rapid development of recombinant TNFR-IgG1 protein with tailored solubility, half-life and antigenicity properties.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (703) 308-7991. The examiner can be reached between the hours of 7:30 am and 4:00 pm Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, Donna Wortman, Primary Examiner can be reached at (703) 308-1032 or the examiner's supervisor, Lynette Smith, can be reached at (703)308-3909.

DONNA WORTMAN
PRIMARY EXAMINER

Robert A. Zeman

May 17, 2001